

A low-rank based estimation-testing procedure for matrix-covariate regression

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Abstract

Matrix-covariate is now frequently encountered in many biomedical researches. It is common to fit conventional statistical models by vectorizing matrix-covariate. This strategy, however, results in a large number of parameters, while the available sample size is relatively too small to have reliable analysis results. To overcome the problem of high-dimensionality in hypothesis testing, variance component test has been proposed with promise detection power, but is not straightforward to provide estimates of effect size. In this work, we overcome the problem of high-dimensionality by utilizing the inherent structure of the matrix-covariate. The advantage is that estimation and hypothesis testing can be conducted simultaneously as in the conventional case, while the estimation efficiency and detection power can be largely improved, due to a parsimonious parameterization for the coefficients of matrix-covariate. Our method is applied to test the significance of gene-gene interactions in the PSQI data, and is applied to test if electroencephalography is associated with the alcoholic status in the EEG data, wherein sparse effects and low-rank effects of matrix-covariates are identified, respectively.

1 Introduction

Matrix-covariate is now frequently encountered in many biomedical researches. Let Y be the response of interest and $\mathbf{M} \in \mathbb{R}^{p \times q}$ be the $p \times q$ matrix-covariate. The research aim focuses on the association between Y and \mathbf{M} , possibly after adjusting the effects of confounding factors $Z \in \mathbb{R}^m$. In the Electroencephalography (EEG) data, for example, Y is the binary alcoholic status, and \mathbf{M} is a 256×64 matrix with its (j, k) -th element $\mathbf{M}(j, k)$ being the voltage value of the k -th electrode measured at the j -th time point. Sometimes, \mathbf{M} is not directly observed but is induced from the original covariates. In the PSQI data, for instance, it is of interest to test if the PSQI score Y is associated with gene-gene interactions ($G \times G$) among one p -genetic markers $G = (g_1, \dots, g_p)^T$ and another q -genetic markers $E = (e_1, \dots, e_q)^T$, i.e., the pq products $\{g_j e_k : 1 \leq j \leq p, 1 \leq k \leq q\}$. In this case, it is equivalent to test if Y is associated with the matrix-covariate $\mathbf{M} = GE^T$ after adjusting for the effects of $Z = (G^T, E^T)^T$, by observing that $\mathbf{M}(j, k) = g_j e_k$.

Two questions are commonly raised by practitioners:

(Q1) Does Y associate with \mathbf{M} ?

(Q2) How does \mathbf{M} affect Y ?

To answer (Q1)-(Q2), a simple method is to fit a GLM for Y on each element of \mathbf{M} , and then use certain method to combine these pq analysis results. This marginal method, however, can produce biased results due to the ignorance of the joint effects of \mathbf{M} . It can also give a low detection power due to a severe penalty from adjusting for multiple hypothesis testing. Joint inference is thus preferable, which fits the GLM

$$Y|(Z, \mathbf{M}) \sim \text{Normal}(E(Y|Z, \mathbf{M}), \sigma^2) \quad (1)$$

for continuous Y with a common variance σ^2 , or

$$Y|(Z, \mathbf{M}) \sim \text{Bernoulli}(E(Y|Z, \mathbf{M})) \quad (2)$$

for binary Y , and assumes that

$$g\{E(Y|Z, \mathbf{M})\} = \gamma + \xi^T Z + \sum_{j,k} \eta_{jk} \mathbf{M}(j, k), \quad (3)$$

where g is the link function, γ is the intercept term, ξ is the effect of Z , and η_{jk} is the effect of $\mathbf{M}(j, k)$. Following the convention, we adopt the identity link $g(u) = u$ for model (1), and adopt the logit link $g(u) = \ln \frac{u}{1-u}$ for model (2). Based on (3), inference about the association between Y and \mathbf{M} relies on the estimation of η_{jk} or testing the null hypothesis

$$H_0 : \eta_{jk} = 0 \quad \forall \quad (j, k). \quad (4)$$

Although the joint method overcomes the problem of bias, it suffers the problem of high-dimensionality, since the number of parameters $1 + m + pq$ can be large in comparison with the sample size n . As a result, statistical inference procedure can be unstable and inefficient, which further decreases the detection power to testing (4).

To overcome the problem of high-dimensionality in testing (4), Lin *et al.* (2013) apply the variance component test (Lin, 1997) to propose GESAT. The authors extend model (3) to the generalized linear mixed model (GLMM) by assuming that η_{jk} 's independently follow an arbitrary distribution with zero mean and a common variance τ^2 . As a result, testing (4) is equivalent to testing $H_0 : \tau^2 = 0$ under the GLMM, and the variance component test is applied. The authors show by simulations that GESAT has higher detection power than the conventional minimum p-value test. GESAT has the advantage of fast computation and is shown to be locally most powerful. GESAT, however, aims to test if Y is associated with \mathbf{M} or not (i.e., answer (Q1)), but is not straightforward to provide estimates of the effect sizes of \mathbf{M} (i.e., answer (Q2)). A naive solution is to fit model (3) to obtain the estimates of η_{jk} 's, but it will again suffer the problem of high-dimensionality, and there is no guarantee that the estimates coincide with the conclusion from GESAT, either. The aim of this study is thus to propose a unified inference procedure to answer (Q1)-(Q2) based on the joint model (3), while overcoming the problem of high-dimensionality.

The rest of this article is organized below. Our improved inference procedure for η_{jk} 's is developed in Section 2, based on which two powerful test statistics for (4) are proposed in Section 3. Section 4 conducts numerical studies to evaluate the performances of our proposal, and Section 5 conducts analyses for both PSQI and EEG data sets. The paper ends with a discussion in Section 6.

2 The Low-rank Based Inference Procedure for $\boldsymbol{\eta}$

2.1 Model specification

The main idea of our proposal is to utilize the matrix structure of \mathbf{M} , from which it is natural to treat η_{jk} as the (j, k) -th element of the $p \times q$ matrix $\boldsymbol{\eta}$. With this matrix representation, model (3) is equivalently expressed as

$$g\{E(Y|Z, \mathbf{M})\} = \gamma + \xi^T Z + \text{vec}(\boldsymbol{\eta})^T \text{vec}(\mathbf{M}), \quad (5)$$

where $\text{vec}(\cdot)$ is the operator that stacks a matrix into a long vector columnwisely. Under model (5), answering (Q1)-(Q2) relies on estimating the matrix $\boldsymbol{\eta}$ and testing

$$H_0 : \boldsymbol{\eta} = \mathbf{0}_{p \times q}. \quad (6)$$

To proceed, it is reasonable to assume that most of $\eta_{jk} = 0$ in practice. As a result, $\boldsymbol{\eta}$ is also likely to be a low-rank matrix, which enables us to impose a parsimonious assumption on $\boldsymbol{\eta}$ to improve efficiency. It motivates us to consider the rank- r GLM model

$$g\{E(Y|Z, \mathbf{M})\} = \gamma + \xi^T Z + \text{vec}(\boldsymbol{\eta})^T \text{vec}(\mathbf{M}) \quad \text{with} \quad \boldsymbol{\eta} = \mathbf{A}\mathbf{B}^T, \quad (7)$$

where $\mathbf{A} \in \mathbb{R}^{p \times r}$ and $\mathbf{B} \in \mathbb{R}^{q \times r}$ with a pre-specified $r \leq \min\{p, q\}$ such that $\text{rank}(\boldsymbol{\eta}) = r$. One advantage of model (7) is the parsimony of parameters. In fact, the conventional model (3) requires $1 + m + pq$ parameters, while it is $1 + m + (p + q)r$ for model (7). When r is small, we would expect an efficiency gain when fitting model (7) and, hence, a higher detection power to testing (6).

Model (7) has been studied in Hung and Wang (2013) (with the logit link function and $r = 1$) and Zhou, Li, and Zhu (2013) (with arbitrary link function and r). Note that using $\boldsymbol{\eta} = \mathbf{A}\mathbf{B}^T$ is overparameterized. This can be seen from $\mathbf{A}\mathbf{B}^T = \mathbf{A}\mathbf{C}\mathbf{C}^{-1}\mathbf{B}^T$ for any nonsingular $\mathbf{C} \in \mathbb{R}^{r \times r}$. As a result, we only require

$$s_r = 1 + m + (p + q - r)r \quad (8)$$

parameters for the rank- r model (7). For the sake of identifiability, both Hung and Wang (2013) and Zhou, Li, and Zhu (2013) impose extra constraints on (\mathbf{A}, \mathbf{B}) . We should note

that the imposed constraints are not unique. The authors of both papers also mention that the choice of the constraint relies on the prior knowledge about the underlying study. Unfortunately, different constraints will produce different analysis results, which is not a desired property in practice. To avoid ambiguity, we leave (\mathbf{A}, \mathbf{B}) arbitrary to develop our method. This is achievable since we are interested in $\boldsymbol{\eta}$ instead of (\mathbf{A}, \mathbf{B}) , and only the identifiability of \mathbf{AB}^T is required. We will also show that the asymptotic properties for the estimator of $\boldsymbol{\eta}$ is invariant to the choice of the identifiability constraints. Consequently, we are allowed to use the convenient parameterization $\boldsymbol{\eta} = \mathbf{AB}^T$ without imposing any constraint on (\mathbf{A}, \mathbf{B}) , which makes our method more applicable in practice.

Remark 1. *The idea of treating $G \times G$ as a matrix $\mathbf{M} = GE^T$ is motivated from Hung et al. (2015), who propose a multistage screening procedure to identify $G \times G$. Our method is more general in that the developed inference procedure is also applicable to the case of binary Y . Moreover, we focus on the problem of testing (6), for which the method of Hung et al. (2016) cannot be directly applied.*

2.2 Estimation and implementation

Some notation are defined first for the ease of reference. Let the data $\{(Y_i, Z_i, \mathbf{M}_i)\}_{i=1}^n$ be random copies of (Y, Z, \mathbf{M}) . Let $X_i = (1, Z_i^T, \text{vec}(\mathbf{M}_i)^T)^T$ be the vector of covariates, and let \mathbf{X} be the $n \times (1 + m + pq)$ data matrix with the i -th row being X_i^T . Let $\theta = (\gamma, \xi^T, \text{vec}(\mathbf{A})^T, \text{vec}(\mathbf{B})^T)^T$ be the parameters of model (7), and let the induced parameters of interest be

$$\beta(\theta) = (\gamma, \xi^T, \text{vec}(\mathbf{AB}^T)^T)^T, \quad (9)$$

which consists of the intercept, the effect of Z , and the effect of \mathbf{M} .

The log-likelihood function of θ (apart from constant terms) is calculated to be

$$\ell(\theta) = -\frac{1}{2n} \sum_{i=1}^n \{Y_i - \beta(\theta)^T X_i\}^2 \quad (10)$$

under the normal error model (1), and is calculated to be

$$\ell(\theta) = \frac{1}{n} \sum_{i=1}^n Y_i \{\beta(\theta)^T X_i\} - \ln[1 + \exp\{\beta(\theta)^T X_i\}]. \quad (11)$$

under the logistic model (2). To stabilize the estimation process, we propose to estimate θ by the penalized MLE

$$\hat{\theta} = \operatorname{argmax}_{\theta} \left\{ \ell(\theta) - \frac{\lambda}{2} \|\mathbf{A}\|_F^2 \|\mathbf{B}\|_F^2 \right\}, \quad (12)$$

where $\|\cdot\|_F^2$ is the Frobenius norm and $\lambda \geq 0$ is the penalty. Here we use the penalty $\|\mathbf{A}\|_F^2 \|\mathbf{B}\|_F^2$ instead of the convention $\|\mathbf{A}\|_F^2 + \|\mathbf{B}\|_F^2$. The main reason is that $\boldsymbol{\eta} = \mathbf{A}\mathbf{B}^T$ is identifiable while (\mathbf{A}, \mathbf{B}) are not. Finally, the parameter of interest is estimated by

$$\hat{\beta} = \beta(\hat{\theta}) = (\hat{\gamma}, \hat{\xi}^T, \operatorname{vec}(\hat{\boldsymbol{\eta}})^T)^T \quad \text{with} \quad \hat{\boldsymbol{\eta}} = \hat{\mathbf{A}}\hat{\mathbf{B}}^T. \quad (13)$$

Note that $\hat{\beta}$ depends on the values of (r, λ) . The rank parameter r determines the accuracy to approximating $\boldsymbol{\eta}$, and we propose to select r as large as possible while preserving the estimation efficiency. In particular, we propose to choose r such that n/s_r is moderately large (e.g., ≥ 5), where s_r is the number of effective parameters defined in (8). For a fixed r , the penalty λ is selected by cross-validation.

To implement our method, we use the alternating method to solve (12). First note that model (7) can be expressed as

$$g\{E(Y|Z)\} = \gamma + \xi^T Z + \operatorname{vec}(\mathbf{A})^T \operatorname{vec}(\mathbf{M}\mathbf{B}) \quad (14)$$

$$= \gamma + \xi^T Z + \operatorname{vec}(\mathbf{B})^T \operatorname{vec}(\mathbf{M}^T \mathbf{A}). \quad (15)$$

Observe that (14) can be treated as the GLM with parameters $\theta_{\mathbf{B}} = (\gamma, \xi^T, \operatorname{vec}(\mathbf{A})^T)^T$ and data $\{(Y_i, Z_i, \mathbf{M}_i \mathbf{B})\}_{i=1}^n$. Thus, when \mathbf{B} is fixed, maximizing (12) with respect to $\theta_{\mathbf{B}}$ becomes the conventional penalized MLE problem with the penalty $\frac{\lambda}{2} \|\mathbf{B}\|_F^2$. The case for fixed \mathbf{A} is similar by using the parameters $\theta_{\mathbf{A}} = (\gamma, \xi^T, \operatorname{vec}(\mathbf{B})^T)^T$, the data $\{(Y_i, Z_i, \mathbf{M}_i^T \mathbf{A})\}_{i=1}^n$, and the penalty $\frac{\lambda}{2} \|\mathbf{A}\|_F^2$. We then iterate the roles of \mathbf{A} and \mathbf{B} until convergence. Detailed implementation algorithm is summarized below.

Alternating method

1. Given an initial value $\mathbf{B}_{(0)}$ from, e.g., the leading r right singular vectors of the conventional ridge estimate of $\boldsymbol{\eta}$. For $k = 0, 1, 2, \dots$, do the following Steps 2-3.

2. Given $\mathbf{B}_{(k)}$, obtain the penalized MLE $(\gamma^*, \xi^*, \mathbf{A}_{(k+1)})$ from (14) using the data $\{(Y_i, Z_i, \mathbf{M}_i \mathbf{B}_{(k)})\}_{i=1}^n$ and the penalty $\frac{\lambda}{2} \|\mathbf{B}_{(k)}\|_F^2$.
 3. Given $\mathbf{A}_{(k+1)}$, obtain the penalized MLE $(\gamma_{(k+1)}, \xi_{(k+1)}, \mathbf{B}_{(k+1)})$ from (15) using the data $\{(Y_i, Z_i, \mathbf{M}_i^T \mathbf{A}_{(k+1)})\}_{i=1}^n$ and the penalty $\frac{\lambda}{2} \|\mathbf{A}_{(k+1)}\|_F^2$. Define $\theta_{(k+1)} = (\gamma_{(k+1)}, \xi_{(k+1)}^T, \text{vec}(\mathbf{A}_{(k+1)} \mathbf{B}_{(k+1)}^T)^T)^T$.
 4. Repeat the procedure until the convergence of $\beta(\theta_{(k+1)})$. Output $\hat{\theta} = \theta_{(\infty)}$.
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2.3 Asymptotic property

We now proceed to derive the asymptotic property of $\hat{\beta}$. Let $\beta_0 = (\gamma_0, \xi_0^T, \text{vec}(\boldsymbol{\eta}_0)^T)^T$ be the true value of β under model (7), and assume the existence of a regular point (Shapiro, 1986) θ_0 in the parameter space of θ such that $\beta_0 = \beta(\theta_0)$. Define

$$\Delta(\theta) = \frac{\partial \beta(\theta)}{\partial \theta} = \begin{bmatrix} \mathbf{I}_{m+1} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & (\mathbf{B} \otimes \mathbf{I}_p) & (\mathbf{I}_q \otimes \mathbf{A}) \mathbf{K}_{q,r} \end{bmatrix}, \quad (16)$$

where $\mathbf{K}_{q,r}$ is the communication matrix satisfying $\mathbf{K}_{q,r} \text{vec}(\mathbf{B}) = \text{vec}(\mathbf{B}^T)$ for any $q \times r$ matrix \mathbf{B} , and let $\Delta_0 = \Delta(\theta_0)$. The asymptotic property of $\hat{\beta}$ is stated below, where its proof is deferred to Appendix.

Theorem 2. *Assume the validity of model (7) with $\beta_0 = \beta(\theta_0)$ and $\text{rank}(\Delta_0) = s_r$. Assume also that $\lambda = o_p(n^{-1/2})$. Then, as $n \rightarrow \infty$, $\sqrt{n}(\hat{\beta} - \beta_0) \xrightarrow{d} N(0, \Sigma_0)$ with the asymptotic covariance matrix $\Sigma_0 = \Delta_0(\Delta_0^T \mathbf{V}_0 \Delta_0)^+ \Delta_0^T$, where \mathbf{V}_0 is defined below:*

(a) For normal model (1), $\mathbf{V}_0 = \sigma^{-2} E[X_i X_i^T]$.

(b) For logistic model (2), $\mathbf{V}_0 = E[\nu_i(\theta_0) X_i X_i^T]$ with $\nu_i(\theta) = \frac{\exp\{\beta(\theta)^T X_i\}}{[1 + \exp\{\beta(\theta)^T X_i\}]^2}$.

The asymptotic property of $\hat{\beta}$ will be the core to develop our test statistics in Section 3, and we propose to estimate the asymptotic covariance matrix Σ_0 by the sandwich-type estimator

$$\hat{\Sigma} = \hat{\Delta} \left\{ \hat{\Delta}^T (\hat{\mathbf{V}} + \lambda \mathbf{I}_{1+m+pq}) \hat{\Delta} \right\}^+ \hat{\Delta}^T \hat{\mathbf{V}} \hat{\Delta} \left\{ \hat{\Delta}^T (\hat{\mathbf{V}} + \lambda \mathbf{I}_{1+m+pq}) \hat{\Delta} \right\}^+ \hat{\Delta}^T, \quad (17)$$

where $\widehat{\Delta} = \Delta(\widehat{\theta})$, $\widehat{\mathbf{V}} = \widehat{\sigma}^{-2} \cdot \frac{1}{n} \sum_{i=1}^n X_i X_i^T$ with $\widehat{\sigma}^2 = \frac{1}{n-s_r} \sum_{i=1}^n (Y_i - \widehat{\beta}^T X_i)^2$ for the case of (1), and $\widehat{\mathbf{V}} = \frac{1}{n} \sum_{i=1}^n \nu_i(\widehat{\theta}) X_i X_i^T$ for the case of (2). Here we add $\lambda \mathbf{I}_{1+m+pq}$ in (17) for the sake of stabilizing estimation, and note that $\widehat{\Sigma} \xrightarrow{p} \Sigma_0$. Consequently, subsequent inference of β_0 can be based on $(\widehat{\beta}, \widehat{\Sigma})$. For example, an approximated $100(1 - \alpha)\%$ confidence interval for the j -th element of β_0 can be constructed as

$$\widehat{\beta}_j \pm \frac{z_{1-\alpha/2}}{\sqrt{n}} [\widehat{\Sigma}]_j^{1/2}, \quad (18)$$

where $[\widehat{\Sigma}]_j$ denotes the j -th diagonal element of $\widehat{\Sigma}$, and $z_{1-\alpha/2}$ is the $(1 - \alpha/2)$ -quantile of the standard normal distribution.

3 Detecting the Significance of η

3.1 The low-rank based test statistic

We propose test statistics based on $\widehat{\eta}$ from the low-rank model (7) for the null hypothesis (6), which provides a unified estimation-testing procedure for η . Motivated from Theorem 2, it is natural to use the Wald-type test statistic

$$T_{\text{wald}} = \text{vec}(\widehat{\eta})^T \left\{ [\widehat{\Sigma}]_{\eta}/n \right\}^+ \text{vec}(\widehat{\eta}), \quad (19)$$

where $[\widehat{\Sigma}]_{\eta}$ is the asymptotic covariance matrix of $\text{vec}(\widehat{\eta})$ from $\widehat{\Sigma}$. Note that $[\widehat{\Sigma}]_{\eta}$ is singular due to over-parameterization of the low-rank model, and the generalized inverse is used. Observing that T_{wald} is a weighted sum of the differences $\text{vec}(\widehat{\eta} - \mathbf{0})$, to see if there is enough evidence to reject H_0 . This strategy, however, can be less powerful in testing (6) when η is sparse, as the contribution of differences can be averaged out during summation. In view of this point, an alternative method is to test (6) by the test statistic

$$T_{\text{max}} = \max_{j \in \{m+2, \dots, 1+m+pq\}} \frac{\widehat{\beta}_j^2}{[\widehat{\Sigma}]_j/n}, \quad (20)$$

which is expected to be powerful when η is sparse. Note that T_{max} generalizes the commonly used strategy, the minimum p-value of pq marginal tests, to test (6), in the sense that T_{max} further considers the joint effects among the matrix-covariate \mathbf{M} .

Obviously, T_{wald} and T_{max} have their own merits in testing (6), depending on the sparsity of $\boldsymbol{\eta}$. Ideally, one should choose the test statistic according to the alternative hypothesis, which might not be known a priori. A reasonable strategy is thus to combine $(T_{\text{wald}}, T_{\text{max}})$ to adapt to various situations. There exists many combination methods based on the p-values, but they are not applicable in our case since the limiting distribution of T_{max} is not easy to derive. We thus propose to combine $(T_{\text{wald}}, T_{\text{max}})$ directly via

$$T = T_{\text{wald}} \cdot T_{\text{max}}, \quad (21)$$

and a large value of T indicates a rejection of (6). The advantage of the product combination is that T is less affected by the scale of T_{wald} or T_{max} .

To overcome the problem of high-dimensionality in testing (6), GESAT has been proposed with the test statistic

$$T_{\text{gesat}} = \left\| \sum_{i=1}^n (Y_i - \tilde{\gamma} - \tilde{\xi}^T Z_i) \text{vec}(\mathbf{M}_i) \right\|^2, \quad (22)$$

where $(\tilde{\gamma}, \tilde{\xi})$ are the restricted MLE of (γ, ξ) under H_0 . GESAT is shown to be locally most powerful for $\boldsymbol{\eta}$ in a neighborhood of 0. It thus has superior performance when $\boldsymbol{\eta}$ has weak effect. However, there is no guarantee for its performance otherwise. Considering its local optimality, it is beneficial to further combine T and T_{gesat} via

$$T^* = T \cdot T_{\text{gesat}}. \quad (23)$$

Our simulation results in Section 4 show that, while T and T_{gesat} have comparable performances (depending on the effect size of $\boldsymbol{\eta}$), T^* is generally the best performer.

3.2 Calculation of p-values

Since the null distributions of T and T^* are not straightforward to derive, we propose to use parametric bootstrap to obtain their p-values. The main idea of parametric bootstrap is to generate the null data from model (7) given $(\gamma, \xi, \boldsymbol{\eta}) = (\tilde{\gamma}, \tilde{\xi}, \mathbf{0})$, where $(\tilde{\gamma}, \tilde{\xi})$ are the restricted MLE of (γ, ξ) under H_0 (Bůžková, Lumely, and Rice, 2011). The implementation algorithm is summarized below.

Parametric bootstrap test

1. Conditional on (Z_i, \mathbf{M}_i) , generate $Y_i^{(b)}$ from model (5) with $(\gamma, \xi, \boldsymbol{\eta}) = (\tilde{\gamma}, \tilde{\xi}, \mathbf{0})$ (and with $\sigma^2 = \frac{1}{n-(m+1)} \sum_{i=1}^n (Y_i - \tilde{\gamma} - \tilde{\xi}^T Z_i)^2$ for normal error model). Obtain the test statistic $T^{(b)}$ ($T^{*(b)}$) by fitting model (7) using $\{(Y_i^{(b)}, Z_i, \mathbf{M}_i)\}_{i=1}^n$.
 2. Obtain the p-value as the fraction of $T^{(b)}$'s ($T^{*(b)}$'s) that exceed T (T^*).
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Although parametric bootstrap procedure can be applied in various situations, its performance depends on the randomness of $(\tilde{\gamma}, \tilde{\xi})$. As a result, using parametric bootstrap can only control the type-I error asymptotically. Alternatively, an exact test can be constructed when Z_i vanishes, i.e., when model (3) reduces to

$$g\{E(Y|\mathbf{M})\} = \gamma + \text{vec}(\boldsymbol{\eta})^T \text{vec}(\mathbf{M}) \quad \text{with} \quad \boldsymbol{\eta} = \mathbf{A}\mathbf{B}^T. \quad (24)$$

In this situation, the null data can be simply generated by randomly permuting \mathbf{M}_i to destroy its connection with Y_i . The implementation algorithm is summarized below.

Permutation test

1. Generate $\{\mathbf{M}_i^{(b)}\}_{i=1}^n$ by randomly permutating $\{\mathbf{M}_i\}_{i=1}^n$. Obtain the test statistic $T^{(b)}$ ($T^{*(b)}$) by fitting model (24) using $\{(Y_i, \mathbf{M}_i^{(b)})\}_{i=1}^n$.
 2. Obtain the p-value as the fraction of $T^{(b)}$'s ($T^{*(b)}$'s) that exceed T (T^*).
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We remind the readers that the permutation test cannot be applied in the presence of Z . The main reason is that permuting \mathbf{M} destroys not only its connection with Y but also its connection with Z , which further makes the resulting p-value biased. Both resampling procedures are suggested to obtain the p-value, according to the underlying data structure.

4 Simulation Studies

4.1 Simulation settings

Simulation studies are conducted to evaluate our proposal, where we use the PSQI and EEG data sets (see Section 5 for detailed descriptions) to generate the simulation data:

(PSQI) Let $Z = (G^T, E^T)^T$ and $\mathbf{M} = GE^T$, where $G \in \mathbb{R}^{15}$ and $E \in \mathbb{R}^7$ are randomly generated from the PSQI data (with sample size $n = 400$). Given (Z, \mathbf{M}) , Y is generated from normal error model (5) with $\gamma = 10$, $\xi = (\xi_G^T, \mathbf{0}_{p-5}^T, \xi_E^T, \mathbf{0}_{q-3}^T)^T$, $\xi_G = \mathbf{1}_5$, and $\xi_E = \mathbf{1}_3$, and the specification of $\boldsymbol{\eta}$ is described separately. In this case, the normal error model (7) with $r = 3$ is fitted.

(EEG) The matrix $\mathbf{M} \in \mathbb{R}^{6 \times 6}$ is randomly generated from the EEG data (with sample size $n = 150$). Given \mathbf{M} , Y is generated from logistic model (5) and (24) with $\gamma = 0$, and the specification of $\boldsymbol{\eta}$ is described separately. In this case, the logistic model (7) with $r = 2$ is fitted.

Simulation results are reported with 500 replicates.

4.2 Simulation results: part-1

We evaluate the performances of $(\hat{\beta}, \hat{\Sigma})$ under

$$\boldsymbol{\eta} = \begin{bmatrix} \boldsymbol{\eta}_1 & \mathbf{0}_{2 \times (q-1)} \\ \mathbf{0}_{(p-2) \times 1} & \mathbf{0}_{(p-2) \times (q-1)} \end{bmatrix} \quad \text{with} \quad \boldsymbol{\eta}_1 = \frac{1}{\sqrt{2}} \cdot \mathbf{1}_2.$$

Simulation results are reported in Table 1, which provides the means and standard deviations (SD) of $\hat{\beta}$, and standard errors (SE) from the means of the diagonal elements of $\hat{\Sigma}$ that correspond to $(\gamma, \xi_G, \xi_E, \boldsymbol{\eta}_1)$, and report the averaged mean square error (AMSE) of $(\hat{\beta}_j - 0)^2$ over the rest parameters (with zero values) to summarize the performance of $\hat{\beta}$. One can see that the biases of $\hat{\beta}$ arise under both PSQI and EEG settings, but they are relatively small in comparison with the corresponding SDs. Together with a small value of AMSE, $\hat{\beta}$ is demonstrated to be a consistent estimator of β_0 . Moreover, a similar values

of SDs and SEs support the validity of $\widehat{\Sigma}$ in estimating Σ_0 . It implies that the asymptotic property of the low-rank model (7) approximately holds even when the sample size is not large. In fact, it only requires 80 parameters for model (7) with $r = 3$ instead of 128 in the conventional case, which makes the large sample theory more plausible to be valid.

4.3 Simulation results: part-2

This simulation evaluates the detection powers of T and T^* (at the significance level 0.05) under two types of $\boldsymbol{\eta}$:

- **Sparse $\boldsymbol{\eta}$:** In each simulation run, $\boldsymbol{\eta}$ has zero effects except for 2 randomly selected elements. The values of the 2 selected elements are generated from $c \cdot U$, where $U \in \mathbb{R}^2$ is randomly generated from unit sphere and c is the effect size.
- **Low-rank $\boldsymbol{\eta}$:** $\boldsymbol{\eta}$ has zero effects except for the first two columns. For each simulation run, the non-zero elements are generated from $c \cdot U$, where $U \in \mathbb{R}^{2p}$ is randomly generated from unit sphere and c is the effect size.

The penalty λ is selected by cross-validation over $\{\frac{s_r}{n^{3/2}}, \frac{s_r}{n}, \frac{s_r}{\sqrt{n \log(n)}}\}$ (such that the condition $\lambda = o_p(n^{-1/2})$ is satisfied), where s_r is defined in (8). Figure 1 reports the power functions of T , T^* , and T_{gesat} for testing (6) at different effect sizes c . For fair comparisons, we use the same re-sampling scheme to obtain the p-value of T_{gesat} . One can see that all methods correctly control the type-I errors at 0.05 level, which implies the validity of the re-sampling schemes (parametric bootstrap or permutation) to obtain valid p-values.

Comparing the detection powers for small effect size c , T and T_{gesat} are detected to have comparable performances when $\boldsymbol{\eta}$ is sparse, and T is slightly worse than T_{gesat} when $\boldsymbol{\eta}$ is low-rank, while T outperforms T_{gesat} when c is moderate to large. This is reasonable since the performance of T_{gesat} can only be guaranteed for $\boldsymbol{\eta}$ in a neighborhood of $\mathbf{0}$. We also observe that T has a significant improvement over T_{gesat} when $\boldsymbol{\eta}$ is sparse, which indicates the usefulness of incorporating (20) in T . For the case of low-rank $\boldsymbol{\eta}$, the improvement of T is observed for normal error model, while the difference between T and T_{gesat} vanishes for logistic model. Although T and T_{gesat} have comparable performances, we should note

that T is directly associated with $\hat{\boldsymbol{\eta}}$, from which a unified estimation-testing procedure for $\boldsymbol{\eta}$ is available, while this is not the case for T_{gesat} .

The above observations reflect the fact that both T and T_{gesat} have their own merits in detecting (6), depending on the underlying structure of $\boldsymbol{\eta}$. Moreover, by combining both methods, T^* is detected to be the best performer in all situations. In summary, our simulations indicate the applicabilities of T^* regardless of the forms of $\boldsymbol{\eta}$. It also indicates that, by imposing a low-rank assumption, we can further improve existing methods (such as GESAT) that ignore the matrix structure of $\boldsymbol{\eta}$.

5 Data Analyses

5.1 The PSQI data

The PSQI data set (Lai *et al.*, 2014) includes 359 subjects with an average age of 41 years old (ranges from 18 to 69). The participants consist of 214 females and 145 males. For each subject, markers on 3 genes are collected: RORA (2 markers), RORB(17 markers), and NR1D1 (4 markers). Also collected for each subject are the assessments of sleep quantity from the Pittsburgh Sleep Quality Index (PSQI) of Buysse *et al.* (1989), which consists of seven scores: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction.

In our analysis, we consider the response Y to be the log-transformation of the sum of all PSQI scores (plus one to avoid taking logarithm for 0), and let ROR contains RORA and RORB, which has 19 markers. Let \boldsymbol{M} be the 19×4 matrix of the interactions ROR \times NR1D1, and let Z consist of age and gender as possible confounding factors. Our interest focuses on whether ROR \times NR1D1 are associated with the PSQI scores. Fitting the normal error model (7) with $r = 3$ gives the p-values (from parametric bootstrap test) of T , T^* , and T_{gesat} to be 0.001, 0.006, and 0.173, respectively. Thus, only the low-rank based methods declare that ROR \times NR1D1 are influential to PSQI score. A large p-value of T_{gesat} also indicates that the true $\boldsymbol{\eta}$ may have moderate effect size, so that T_{gesat} has limited detection power to declare its significance.

To further identify the root causes, we report the estimated effect sizes of $\text{ROR} \times \text{NR1D1}$ in Table 2, where the significant effects (identified by the parametric bootstrap test p-values of $\hat{\beta}_j$'s after Bonferroni correction) are marked as bold. In particular, 3 specific interactions among rs1144047, rs1327836, rs2269457, and rs12941497 are identified, which can be the candidate interactions for further investigations. It also indicates a sparse effects of $\text{ROR} \times \text{NR1D1}$ on the PSQI score.

5.2 The EEG data

The EEG data contains 77 subjects in alcoholic group ($Y = 1$) and 45 subjects in control group ($Y = 0$). The measurement of voltage values at 256 time points and 64 channels are collected for each subject. It is interesting in investigating if the EEG signal is associated with the alcoholic status Y . The raw data can be obtained from the UCI Machine Learning Repository (<http://archive.ics.uci.edu/ml/datasets/EEG+Database>).

In our analysis, we use the same data as the one used in Hung and Wang (2013), and follow a similar procedure for data pre-processing. In particular, we first reduce the dimensionality of the original 256×64 matrix-covariates to 10×10 by multilinear principal component analysis (MPCA). See Hung *et al.* (2012) for an illustration of MPCA. The matrix \mathbf{M} is then obtained from the reduced 10×10 matrix after componentwise standardization. Based on (Y, \mathbf{M}) , the logistic model (7) with $r = 2$ is fitted. In this data analysis, T , T^* , and T_{gesat} all produce p-values (from permutation test) $< 10^{-3}$, indicating a strong association between the EEG signals and the alcoholic status. This result confirms the findings from Hung and Wang (2013) and Zhou, Li, and Zhu (2013), who both analyze the EEG data.

To delve into the association between \mathbf{M} and Y , we report the estimates $\hat{\boldsymbol{\eta}}$ in Table 3, where the significant elements (identified by the permutation test p-values of $\hat{\beta}_j$'s after Bonferroni correction) are marked as bold. One can see that most of the effective elements of \mathbf{M} are in the position of its second row. It indicates the influence of the EEG signals should have a low-rank structure, where only a few channels can have functions to alcoholic status over times. We remind the readers that our estimates $\hat{\boldsymbol{\eta}}$ is obtained without imposing any identifiability constraint for the parameterization $\boldsymbol{\eta} = \mathbf{A}\mathbf{B}^T$, while the

results from Hung and Wang (2013) and Zhou, Li, and Zhu (2013) do.

6 Conclusion

In this paper, we propose powerful methods to detect the significance of matrix-covariate. We utilize the matrix structure of $\boldsymbol{\eta}$ to achieve a parsimonious parameterization and, hence, a higher detection power than conventional methods. Our proposal is different from existing methods in that no identifiability constraint is required when making inference about $\boldsymbol{\eta}$. Another advantage is that our method can provide estimates of $\boldsymbol{\eta}$ at the same time. By reporting $\hat{\boldsymbol{\eta}}$, we identify a sparse effect of $G \times G$ in the PSQI data, while a low-rank effect is detected in the EEG data.

The matrix-covariate discussed in this work is an order-two tensor. Tensor-covariate can be found in many applications nowadays. For example, p covariates measured at q time points under k environments corresponds to an order-three tensor (with dimension $p \times q \times k$) for each subject. Statistical inference procedure for GLM with tensor-covariate has been developed in Zhou, Li, and Zhu (2013) and Zhou and Li (2014), where the authors focus on the estimation of the effect size of tensor-covariate. When the research aim is to test the existence of association between the response and tensor-covariate, our low-rank based test statistics T and T^* can be extended, provided that a version of the asymptotic property Theorem 2 is developed for tensor-covariate. Another issue is the chosen “low-rank” parameterization of a tensor, which is not unique as in the case of matrix. This can be a future study.

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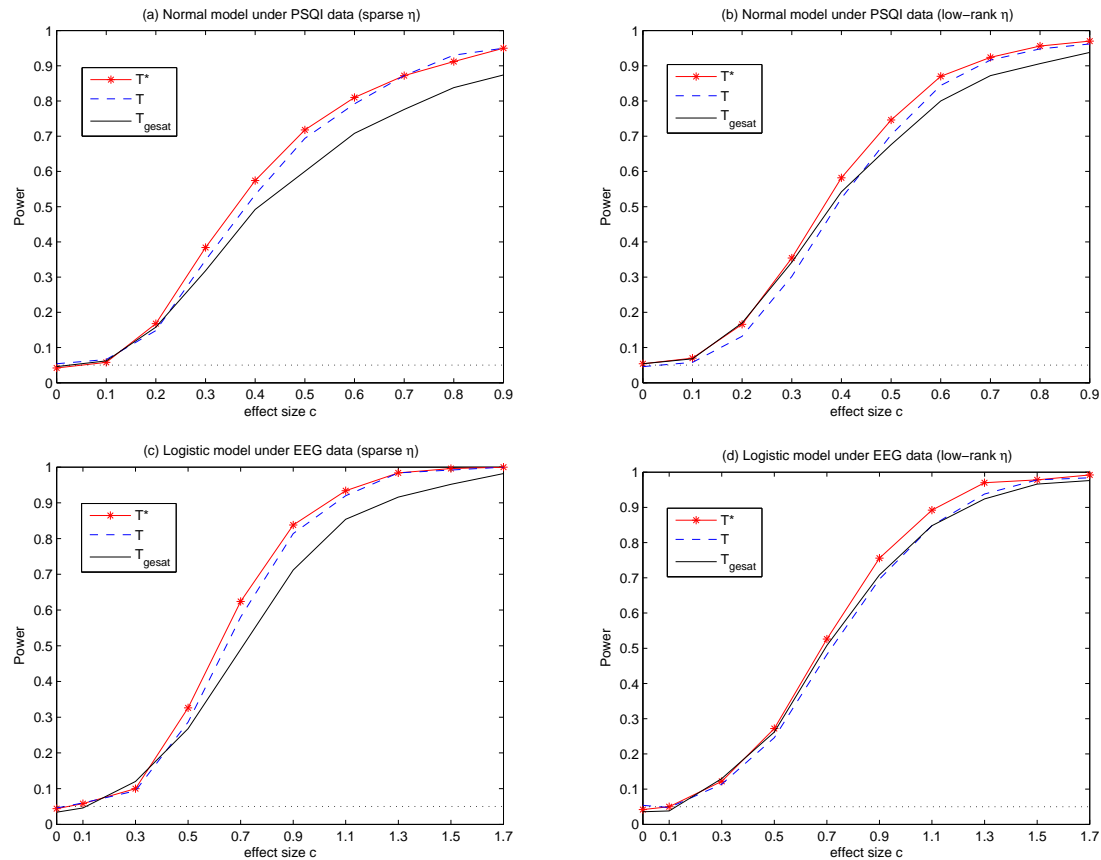


Figure 1: The power functions under two types of η (sparse in the left panel, and low-rank in the right panel) at different effect sizes c . (a)-(b): the normal model using the PSQI data; (c)-(d): the logistic model using the EEG data. The dotted horizontal lines represents the significance level 0.05.

Table 1: The means (Mean) and standard deviations (SD) of $\hat{\beta}$, and the standard errors (SE) from the diagonal elements of $\hat{\Sigma}$. The last row gives the mean and standard deviation of AMSE.

	PSQI				EEG			
	True	Mean	SD	SE	True	Mean	SD	SE
γ	10.000	9.998	0.062	0.059	0.000	-0.002	0.212	0.205
ξ_G	1.000	0.996	0.107	0.104				
	1.000	0.986	0.113	0.104				
	1.000	1.014	0.108	0.103				
	1.000	1.005	0.112	0.103				
	1.000	0.995	0.111	0.102				
ξ_E	1.000	1.005	0.085	0.081				
	1.000	0.994	0.091	0.081				
	1.000	0.998	0.082	0.080				
η_1	0.707	0.638	0.117	0.108	0.707	0.657	0.251	0.220
	0.707	0.631	0.126	0.108	0.707	0.634	0.284	0.233
AMSE		0.008	0.002			0.036	0.013	

Table 2: The effect sizes $\hat{\eta}$ of ROR×NR1D1 from normal model (7) with $r = 3$, where the significant elements are marked as bold.

		NR1D1			
		rs2314339	rs2071427	rs2269457	rs12941497
RORA	rs809736	-0.007	-0.026	-0.019	0.047
	rs4774388	0.001	0.014	0.016	-0.034
RORB	rs10491929	0.002	0.004	0.002	-0.005
	rs17611535	0.001	0.015	0.017	-0.036
	rs10217594	-0.004	0.007	0.016	-0.030
	rs7037043	-0.008	-0.023	-0.014	0.036
	rs2025882	-0.001	-0.004	-0.003	0.006
	rs7022435	-0.001	-0.005	-0.004	0.010
	rs3750420	0.001	0.001	0.000	-0.001
	rs1013078	-0.004	-0.027	-0.026	0.059
	rs2273975	-0.004	0.012	0.023	-0.044
	rs3903529	0.003	-0.004	-0.011	0.020
	rs11144041	0.004	0.006	0.000	-0.003
	rs7021908	-0.002	0.000	0.004	-0.006
	rs7865407	-0.003	-0.012	-0.009	0.022
	rs11144047	-0.007	-0.040	-0.036	0.083
	rs1327836	0.005	0.054	0.058	-0.125
	rs11144064	-0.001	-0.005	-0.004	0.010
	rs4098048	0.003	0.000	-0.005	0.008

Table 3: The effect sizes $\hat{\eta}$ of EEG from logistic model (7) with $r = 2$, where the significant effects are marked as bold.

0.063	-0.113	0.059	-0.026	-0.008	-0.015	-0.029	-0.009	0.031	-0.035
-0.108	0.217	-0.133	0.068	-0.023	0.018	0.016	-0.070	-0.073	0.112
0.074	-0.170	0.119	-0.067	0.047	-0.005	0.018	0.120	0.068	-0.121
0.004	-0.021	0.022	-0.015	0.020	0.003	0.017	0.046	0.014	-0.031
0.049	-0.102	0.064	-0.034	0.015	-0.007	-0.003	0.042	0.036	-0.057
0.056	-0.110	0.066	-0.033	0.008	-0.010	-0.012	0.028	0.036	-0.053
0.008	-0.042	0.045	-0.031	0.041	0.007	0.035	0.096	0.028	-0.064
-0.033	0.068	-0.042	0.022	-0.008	0.005	0.004	-0.024	-0.023	0.036
-0.021	0.050	-0.035	0.020	-0.014	0.002	-0.006	-0.036	-0.020	0.036
0.038	-0.067	0.034	-0.015	-0.006	-0.009	-0.019	-0.008	0.018	-0.019